

Efficacy of a strategy to prevent neonatal early-onset group B streptococcal (GBS) sepsis

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Abstract

Background: Existing guidelines recommend different strategies to prevent early-onset neonatal GBS sepsis. In 1997, using our own data on incidence and risk factors, we established a new prevention strategy which includes GBS screening at 36 weeks' gestation and intrapartum antibiotic prophylaxis (IAP) in women with positive or unknown GBS colonization with at least one risk factor. The present study evaluates the efficacy of the new prevention strategy.

Methods: Retrospective study of the incidence of early-onset GBS sepsis among all live births at the University Women's Hospital Basel between 1997 and 2002. Additional analysis of delivery and post partum period of all GBS sepsis cases, including GBS screening, risk factors during labor (prematurity, rupture of membranes (ROM) < 12 h, intrapartum signs of infection), and IAP. Comparison of this group's characteristics G2 (9,385 live births, using the new strategy) with the previous group, G1 (1984–1993, 16,126 live births, without GBS screening or routine IAP) was performed.

Results: The incidence of early-onset GBS sepsis was reduced from 1/1000 (G1) to 0.53/1000 (G2). We observed a significant reduction of overall intrapartum risk factors in cases of GBS sepsis.

Conclusion: This study suggests that our new prevention strategy is effective in reducing the incidence of early-onset GBS sepsis in neonates. In comparison, implementation of the CDC's prevention strategy might have prevented 2 additional cases in 9385 live births. However, this would have required treating a much larger

number of pregnant women with IAP with consequential increasing costs, side effects and complications.

Keywords: Antibiotic prophylaxis; early onset sepsis; female; group B streptococcus; newborn; pregnancy complications; risk factors; streptococcal infections/pc [prevention & control]; streptococcus agalactiae; Switzerland.

Introduction

Group B streptococcus (GBS) first emerged as an important pathogen in the 1970s. Subsequently, early-onset GBS sepsis (in infants less than seven days old) became the leading cause of sepsis in newborns and one of the most common causes of neonatal infectious morbidity and mortality [13, 18].

At any given time, between 10 and 30% of women in the United States are colonized with GBS [18, 26]. The prevalence of colonization in Switzerland, as in other European countries, is 5–15% [23–25]. Although GBS colonization in the gastrointestinal and genital tracts of women is most often asymptomatic, transient and does not require treatment, GBS can nevertheless cause urinary tract, skin, and soft tissue infections (including chorioamnionitis, endometritis and postpartum wound infections), or sepsis [12, 18]. During delivery, maternal vaginal colonization with GBS is an important risk factor for early-onset neonatal GBS sepsis. About half of the infants born to colonized mothers become colonized on their skin and mucosal surfaces as a result of passing through the birth canal or from GBS ascending into the amniotic fluid. One to two percent of the colonized infants will develop early-onset disease. GBS sepsis has been reported in 0.2–3.0/1000 births in the US and in some European countries [20, 23]. Mortality between 4 and 10% and neurological sequelae, such as long-term hearing loss, impaired vision, and developmental problems in 10–20% are observed [18, 20, 23].

In addition to maternal GBS carrier status, prematurity (onset of labor < 37 completed weeks), prolonged rupture of membranes (ROM > 18 h after onset of labor), or intrapartum fever (> 100.4°F/38°C) have been identified as risk factors for early-onset neonatal GBS sepsis. GBS bacteriuria during a current pregnancy reflects heavy colonization and is considered a risk factor, as is a previous delivery of an infant with early-onset GBS sepsis [12, 18].

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Table 1 Risk-based versus Screening-based approach to prevent neonatal early-onset GBS sepsis as recommended by CDC in 1996 [2].

Screening	Risk-based	Screening-based
	No	35–37 weeks gestation
Risk factors	<ul style="list-style-type: none"> – Prolonged ROM (> 18 h) – Preterm delivery (<37 weeks gestation) – Maternal intrapartum fever (> 100.3°F or 37.9°C) – GBS bacteriuria – Previous neonate with early-onset GBS sepsis 	Same as in risk based approach
IAP	<ul style="list-style-type: none"> – If risk factor present – If GBS bacteriuria or previous neonate with early-onset GBS sepsis 	If GBS positive independent of risk factor If GBS unknown and presence of risk factor

Since 1992, international attempts have been made to establish guidelines for preventing early-onset neonatal GBS sepsis [2, 10, 24]. Detection of maternal GBS carrier status and/or of intrapartum risk factors have been the main focus in these guidelines (Table 1). Asymptomatic colonization can be determined by culturing the bacteria from the vagina and the rectum. Culturing techniques have recently improved, and prenatal cultures taken late in pregnancy (35–37 weeks) can predict colonization status at delivery [26]. Timely detection of maternal colonization during labor is not currently feasible, given the low reliability of commercially available rapid tests [11]. Intrapartum antibiotic prophylaxis (IAP) with penicillin as the first line agent, administered to women at risk for transmitting GBS to their newborns, has been shown to decrease the risk of vertical transmission and early-onset neonatal GBS sepsis [5, 18, 22]. However, concerns related to IAP include costs, allergy (including anaphylactic reactions) and microbial resistances [9, 18, 23].

In 1995, aiming for prevention of early-onset neonatal GBS sepsis, we determined the incidence of this complication in our live births between 1984 and 1993, and evaluated the risk factors among the affected cases [24]. Based on our results, and taking into consideration above mentioned concerns, we developed a new strategy to prevent neonatal GBS sepsis, which was implemented in our department in 1997. We established screening between 35 and 37 weeks' gestation and gave IAP in GBS carriers who had an additional risk factor (rupture of membranes more than 12 h, preterm delivery and intrapartum signs of infection). IAP was also given in case of unknown GBS colonization when another risk factor was present, or in case a previous infant had contracted GBS sepsis.

According to the revised CDC Guidelines from 2002, the benefits of a screening-based approach (general screening for GBS colonization, all women with positive culture receive IAP) outweigh the above mentioned concerns and is superior to a risk-based approach (IAP is given in the presence of risk factors without screening) [18]. The present study aimed to evaluate the efficacy of our screening and risk-factor directed strategy.

Material and Methods

Population and study design

We conducted a retrospective analysis in order to determine the incidence of early-onset GBS sepsis among all live births at the University Women's Hospital Basel between 1997 and 2002. In addition, analysis of delivery and postpartum period of the GBS sepsis cases was performed. GBS carrier status, risk factors during labor and IAP were noted. This group (G2) of 9,385 live births had been managed by following our prevention management, implemented in 1997, which consisted of GBS screening at 35–37 weeks gestation (swab taken from the lower third of the vagina, and processed using selective broth medium), risk factor detection and administration of IAP in the presence of GBS or unknown colonization plus an additional risk factor (Table 2), or in case a previous child had contracted GBS sepsis. We further compared our findings in this group (G2) with data collected from another group of neonates (G1), born before this new prevention management had been established. G1 included 16,126 live births during the years 1984–1993. Women in G1 had not been screened for GBS and had not received routine IAP.

Data collection

Cases of early-onset GBS sepsis were identified from the data bank of the department of pediatrics as well as of the microbiology laboratory. Early-onset neonatal GBS sepsis was defined as a positive blood culture with clinical symptoms appearing within 7 days postpartum. Bacterial identification was established according to the Manual of Clinical Microbiology following NCCLS Guidelines of susceptibility testing [15]. The labor and delivery records of the affected infants and their mothers were reviewed. Summarized information for the cases included the following variables: gestational age, GBS screening, clinical risk factors (Table 2), previous infant with GBS sepsis, IAP, maternal intra- and postpartum morbidity, and neonatal mortality. The period between onset of labor or the ruptures of the membranes and delivery was defined as the "intrapartum" period.

Statistical analysis

The software of Epi Info Version 3.2 [8] was used to calculate risk ratios and their confidence intervals. For further testing of significance the Chi-square test was used, and the 2-tailed Fis-

Table 2 Management for prevention of neonatal early-onset GBS sepsis before and after introduction of a new prevention strategy.

Group	G1 (1984–1993, 16,126 live births)	G2 (1997–2002, 9,385 live births)
Management	No screening No routine IAP	GBS screening at 35–37 weeks' gestation IAP in case of: <ul style="list-style-type: none"> – Positive or unknown GBS carrier status and the presence of at least one intrapartum risk factors (ROM > 12 h, delivery < 37 weeks, maternal intrapartum signs of infection (temperature $\geq 38^{\circ}\text{C}$, CRP ≥ 20 mg/L, Leukocytosis $\geq 18,000/\mu\text{L}$, or persistent fetal tachycardia) – Previous neonate with early-onset GBS sepsis

her's exact test was used when the expected cell value was less than 5.

Results

The present study at the University Women's Hospital Basel evaluated the incidence of early-onset neonatal GBS sepsis in a total of 25,511 live births between the years 1984–1993 (G1, 16,126 live births) and 1997–2002 (G2, 9,385 live births). Twenty-one cases were identified, of which 16 occurred in G1, before prevention management had been implemented (Table 3). After implementation of the prevention strategy we observed 5 cases out of 9,385 live births. The incidence of early-onset GBS sepsis decreased from 1/1000 (G1) to 0.53/1000 live births (G2), and the Relative Risk (RR) of developing GBS

sepsis in G2 was 0.54 times the risk observed in G1. The 95% confidence interval (CI), however, included 1 (0.20–1.47), which was reflected in the statistically not significant Chi-square test ($P=0.217$) (Figure 1).

Table 3 compares the characteristics of early-onset neonatal GBS sepsis between the two groups. As a result of establishing a management in which women with positive or unknown GBS colonization and at least one risk factor for GBS sepsis received IAP, we observed significantly fewer risk factors present during delivery of the neonates who developed GBS sepsis (Fisher exact test, $P<0.001$). Particularly, reduction of ROM < 12 h reached statistical significance (Fisher exact test: $P=0.01$). The carrier status was still unknown in one of 5 term-born cases of neonatal GBS sepsis in G2 indicating incomplete implementation of screening. None of the 5 cases

Table 3 Comparison of early-onset neonatal GBS sepsis between the two groups G2 & G1.

	G1	G2	P-values
Time period	1984–1993,	1997–2002	
Live births (n)	16,126	9,385	
Cases of GBS sepsis	16	5	
Characteristics of cases and their mothers:			
GBS colonization in cases	16 × unknown	2 × positive 2 × negative 1 × unknown	
Risk factors**:	15/16	0/5	$P \leq 0.001^*$
Premature delivery	7/16	0/5	$P=0.12$
Rupture of Membranes > 12 h	11/16	0/5	$P=0.01^*$
Signs of amnionitis	7/16	0/5	$P=0.12$
IAP	0/16	0/5	
Mortality	1/16	0/5	$P=1$
Mean gestational age (weeks)	37	40+2	
Mean interval until positive blood culture (days post partum)	1.7	1.6	
Postpartum infection	7/16	0/5	$P=0.12$

*P-values statistically significant ($P<0.05$).

** Women may have had more than one risk factor.

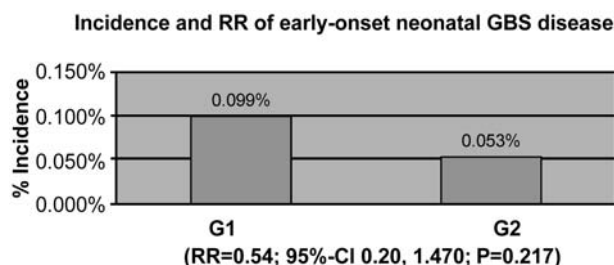


Figure 1 Incidence and RR of early-onset neonatal GBS sepsis in G1 compared to G2.

had an indication for IAP according to our management and none received IAP. The case-fatality decreased from one case, a preterm delivery, in G1 to no case in G2.

Two of the five infants who developed early-onset GBS sepsis were born to mothers who had been screened GBS positive. The first case was a male neonate, 3065 g, born at 39+0 weeks gestation, by vacuum extraction for bradycardia. He had good APGAR (9/10/10) scores and cord blood pH, and initially appeared healthy. However, subsequently he developed vomiting, gray skin, and his CRP was increased. GBS was found in his blood culture four days after delivery. Antibiotic therapy resulted in rapid recovery. The second case was a male neonate, 4550 g, born at 41+1 weeks gestation, by vacuum extraction for macrosomia and non-reassuring fetal monitoring. Amniotic fluid contained meconium. APGAR scores were 1, 7 and 10, and cord blood pH was good. Soon after delivery, the neonate developed tachypnea and became pale. His blood culture one day later showed GBS. Antibiotic therapy with Augmentin and Fortam resulted in gradual recovery.

Discussion

Early-onset group B streptococcal sepsis has been the leading cause of neonatal sepsis and one of the most common causes for neonatal infectious mortality in the USA and Switzerland since the 1970s. Newly developed prevention strategies with intrapartum antimicrobial prophylaxis (IAP) effectively prevent the disease [2, 5, 18, 22]. However, concerns have been raised regarding costs, side effects and complications from these strategies; particularly screening and widely use of IAP [9, 18]. The focus has been on how to best identify mothers and infants at risk for being infected and women who should receive intrapartum antibiotics.

In 1997 we implemented a new prevention strategy, which was based on our own results regarding incidence of early-onset neonatal GBS sepsis and its risk factors in 16,126 live births at our institution between 1984 and 1993 (G1) [24]. We established a screening program between 35 and 37 weeks' gestation and administered IAP in GBS carriers only if they had an additional risk

factor (ROM more than 12 h, preterm delivery and maternal intrapartum signs of infection). IAP was also given in case of unknown GBS status in the presence of a risk factor, or in case a previous child had contracted GBS sepsis (Table 2). The evaluation of 9,385 live births (G2, between 1997 and 2002) managed with our new strategy, showed a decrease in the incidence of early-onset GBS sepsis from 1/1000 (G1) to 0.53/1000 live births (G2). This decrease was reflected in a RR of 0.54 in G2 compared to G1. However, the 95% confidence interval (CI) included 1 (0.20–1.47), and the p-value was not statistically significant ($P=0.217$) (Figure 1). This lack of statistical significance of the result might be due to low power, a limitation often encountered in the presence of a rare disease.

Before the introduction of the US national guidelines, an incidence of 2–3 cases of early-onset neonatal GBS sepsis per 1000 live births was reported [18]. In 1996, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention (CDC) issued guidelines for prevention, and recommended the use of either a risk-based or a screening-based approach to identify women for IAP (Table 1) [2]. Implementation of the first guidelines coincided with a 65% decline in the incidence of GBS sepsis between 1993 and 1998 (from 1.7 to 0.6/1000 live births) [20].

Similar to our results, an evaluation of the 1996 Guidelines which included a large retrospective cohort study, revealed an overall incidence of 0.5/1000 live births [19]. Fifty-two percent of women in the cohort had been screened for GBS. Further analysis showed that the risk of GBS sepsis was significantly ($<50\%$) lower among infants of screened women than among those in the risk-based group (adjusted RR 0.46; 95% CI 0.36, 0.6). Projections showed that 100% implementation of the risk-based approach would have reduced the incidence from 0.5/1000 to 0.44/1000 live births, whereas a 100% implementation of screening-based approach would have led to a further reduction with only 0.32 infections per 1000 live births (95% CI 0.26, 0.38) [19]. Based on the evaluation, revised guidelines were published in 2002, favoring the screening-based approach [1, 3, 4, 19]. By following this screening-based approach and giving IAP to all GBS positive women, we could have potentially prevented 2 cases of sepsis and would have reduced the incidence to the 0.32/1000 live births in our population (G2). This low incidence had been projected by Schrag et al. in 2002 [19] and was observed in the US in 2003 [6, 16].

Schrag et al. [19] observed that in women with a positive GBS culture but without an additional risk factor, who did not receive IAP, the incidence of disease was 1.3/1000 live births (95% CI 0.3, 2.8). The higher the percentage of these women in an obstetric population, the more the overall incidence would approach 1.3/1000.

Even though we follow the same management, our incidence of GBS sepsis is much lower than 1.3/1000 live births, probably because of the relatively lower prevalence (10–15%) of GBS colonization in Switzerland compared to the 10–30% reported in the US [18, 23, 24].

Availability of European data about maternal GBS colonization and incidence of neonatal GBS sepsis is limited. Colonization in most European countries ranges from 10 to 20% [25]; and respectively from 10 to 15% in Swiss women [23–25]. A limitation of the present study is that it was impossible to extract the percentage of GBS screened women and the prevalence of GBS among our study population from the charts.

In accordance with our findings, early-onset GBS sepsis in Europe develops in 0.3–2/1000 live births [25]. Many European countries, including Switzerland, lack national GBS sepsis prevention guidelines, but have local protocols [25]. The German Society for Obstetrics and Gynecology has adopted the CDC guidelines for prevention of GBS sepsis in 2004, but recommend an evaluation of this management 2–3 years after its implementation [7].

Further analysis showed that in accordance with our new prevention guidelines none of our 5 GBS sepsis cases in G2 had an indication for IAP, and therefore none received IAP. This is supporting evidence for the actual implementation of our new prevention strategy, also reflected in a significant reduction of the presence of risk factors in the cases compared to cases in the previous time period (G1). GBS colonization was still unknown in one of 5 term-born cases of neonatal GBS sepsis in G2, indicating incomplete implementation of screening. Since the CDC guidelines are complex, noncompliance has been reported frequently; in up to 39% of cases with the risk-based approach and 14% with the screening-based approach. A US survey published in 2000 showed that 98% adopted a GBS policy, of which 69% used a version of a screening approach and 26% used the risk-based approach. Hospitals with any intensified prevention policy had a significant decline in incidence of early-onset disease [9, 19].

Our case-fatality decreased from one case, a preterm delivery in G1 to none in G2. Due to improved neonatal care, the survival of GBS sepsis improved in recent years (from initially 50 to now 96%), but continues to be lower in preterm infants [5, 9].

Concerns about an optimal management are due to costs of screening and IAP, as well as adverse effects of IAP including allergic or anaphylactic reactions to IAP, emergence of antimicrobial resistant GBS strains and other pathogens, and an increased incidence of serious neonatal infections caused by pathogens other than GBS. Further issues of interest include improvement in screening and development of vaccines [9].

Cost-effective analyses in the US suggested that the risk-based approach is equally cost effective or superior

to the screening-based approach [14, 17]. Rouse et al. [17] calculated an 18% maternal treatment rate in the risk-based approach, and 27% in the screening-based approach. In both strategies total costs were estimated to be similarly low. In contrast, Schrag et al. [19] showed that the anticipated intrapartum antibiotic use did not differ between the screening and risk-based strategies, when the both were implemented according to the CDC recommendations. Under screening, an estimated 30% of deliveries received intrapartum antibiotics for any reason whereas under the risk-based approach 29% received intrapartum antibiotics for any reason. Under each strategy 24% of deliveries had an indication for GBS prophylaxis. The authors did not present a cost-effective analyses, but were in favor of the screening-based approach, since it allowed for a broader coverage of the at-risk population, capturing colonized women without obstetric risk factors (18% of deliveries), which resulted in a lower incidence of GBS sepsis compared to the risk-based approach [19]. We assume that by following our management we used less IAP than in either the screening-based approach favored by CDC or the pure risk-based approach, since we did not treat GBS-negative women even if presenting with risk factors, nor GBS-positive women without additional risk factor. However, in our study we could not obtain the actual frequency of IAP. Ideally, the data on GBS screening and prevalence, as well as IAP, would be collected in a prospective study. A Swiss prospective cohort study based on cost-benefit analysis came to an even more extreme conclusion. It suggested that even though both the risk- and screening-based approaches recommended by the CDC were more effective than their restrictive risk-based approach, these approaches implied increased hospital costs and a substantial increase in the proportion of women receiving antibiotics during labor, which may be unjustified in a setting of low maternal GBS carrier status. They reported an incidence of only 0.4/1000 live births, while only treating 6.0% of women with antibiotics during labor. Adopting the risk-based approach as defined by the CDC they would have expected to treat 13.5% women and 16.5% with the screening-based approach [23].

Wide use of antibiotics has been criticized for several reasons. Resistance to clindamycin and erythromycin increased among GBS isolates. Concerns have also been raised regarding an emerging resistance of second line agents. Most studies find stable or declining rates of sepsis caused by other pathogens, whereas selected populations, such as preterm and very low birth weight neonates seem to be at a higher risk for sepsis caused by resistant microorganisms [9, 21]. Data on changing prevalence in resistant pathogens, i.e., *E. coli*, which cause illness outside the context of the labor and delivery setting, are controversial [21].

Our results showed two cases of GBS sepsis in negatively screened women. This may be explained by a pre-

vious observation in which 15–20% of all women who had negative second trimester cultures were subsequently colonized in the late third trimester or during delivery [26]. Based on this concern, there has been a great interest in development and implementation of rapid and sensitive techniques to screen for GBS colonization and antibiotic susceptibility until effective vaccines against GBS are available for clinical use [9, 16, 21]. Vaccine development has reached phase I and II, but proceeding to phase III has turned out to be difficult, due to liability issues if tested in pregnant women [9].

In summary, our management of screening all women, but administering IAP only in women with an unknown or positive GBS culture who have an additional risk factor, intends to reduce the use of antibiotics compared to the screening-based approach suggested by the CDC. The advantage of our management versus a pure risk-based approach without screening is that IAP can be tailored to women with a positive culture and risk factors, versus treating everyone with a risk factor in the absence of screening. Thereby, we exclude many women from IAP. IAP causes more harm than screening, since in addition to costs, which results from screening as well as from IAP, IAP has adverse affects including allergic reactions and emergence of resistant pathogens. With this approach we successfully decreased our incidence of early-onset neonatal GBS sepsis to 0.53/1000 live births. In order to reach the most recent reported incidence of 0.32/1000 live births in the US, we would have to adopt the screening-based approach currently recommended by CDC. However, this would mean giving IAP to many more pregnant women. Our data suggest that guidelines developed for the setting present in the US should not be adopted uncritically, and that a modified strategy of the CDC guidelines can be appropriate in a setting of lower prevalence of GBS colonization. Without any doubt, development of effective rapid tests and GBS vaccines remain a priority.

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